Amendments to the Drawings:

The attached sheets of drawings includes changes to Figures 3B and 14. These sheets replace the corresponding original sheets. In each of Figures 3B and 14, the previously omitted sequence identifiers have been added.

Attachment: Replacement Sheet

Annotated Sheet Showing Changes

II. RESPONSE TO OFFICE ACTION

A. *Status of the Claims*

Claims 1-57 were pending prior to the Office Action dated April 10, 2006. Claims 7, 13, 14, 26, 28-31, 40, 41 and 47-57 have been withdrawn pursuant to the Response to Restriction Requirement dated June 17, 2005. Claims 1, 3, 5, 8, 12, 22, 25, 39 and 44 have been amended. The contents of claim 4 have been incorporated into claim 1 in the amendment contained herein, and claim 4 has been cancelled. Support for the amendments may be found throughout the specification, and more particularly, in the figures. No new matter has been added. Thus, claims 1-6, 8-12, 15-25, 27, 32-39 and 42-46 are presently pending.

B. *Objections to the Specification, Drawings and Claim 39*

1. *The Specification is Proper*

The Action objects to the specification because it contains embedded hyperlinks and/or other forms of browser-executable codes. Applicant has amended these references in the amendment herein.

The Action further objects to the specification for the improper disclosure of polypeptide sequences for failing to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. Applicants have amended the specification accordingly in the amendment herein, and have provided a CD disclosing the corresponding SEQ ID NOs.

In light of the above, Applicants respectfully request the objections to the specification be withdrawn.

2. *Corrected Drawings*

The Action objects to the drawings submitted on August 15, 2001, because Figures 3B and 14 improperly disclose polypeptide sequences, as they fail to comply with the requirements

of 37 C.F.R. §§ 1.821 through 1.825. Applicants submit herein replacement drawings and respectfully request the objection to the drawings be withdrawn.

3. Claim 39 Is Proper

The Action objects to claim 39 for improper disclosure of polypeptide sequences, as it fails to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. Applicants note that claim 39 now reads as follows: "The method of claim 38, wherein the peptide comprises the sequence VKIKK (SEQ. ID NO: 11)." Applicants believe that amended claim 39 complies with the requirements of 37 C.F.R. §§ 1.821 through 1.825 and respectfully request the objection be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 22, 23, 44 and 45 are rejected as being indefinite under 35 U.S.C. § 112, second paragraph, for reciting the term DAP1 as the sole means of identifying the claimed PPT1 modulator. Applicants note that the claims have been amended to recite the following: "...wherein the peptide is DAP1 (AcG-palmitoyl diaminopropionate-VKIKK (SEQ ID NO: 11))." Support for this claim can be found in the specification. *See, e.g.*, page 7, lines 11-12. By making this amendment, Applicants in no way concede that the claim, in its previous form, was indefinite.

Applicants respectfully request reconsideration of these claims and request that the indefiniteness rejection be withdrawn.

D. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

1. The Written Description Rejection Is Overcome

The Action rejects claims 1-6, 8-11, 15-21, 24, 27, 32-38, 42, 43 and 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In part, the Action asserts that the specification fails to provide a representative number of species that

encompass the genus of PPT1 modulators nor does it provide a description of structural features that are common to PPT1 modulators. Applicants traverse.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). In particular, the Federal Circuit has stated that "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ 2d 1227, 1232 (Fed. Cir. 2000). The Federal Circuit has also noted that " [if] a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Appellants note the Examiner's reliance on *Regents of the University of California v. Eli Lilly and Co.*, 119 F. 3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004) appears to be misplaced regarding the written description requirement. In *Lilly*, the specification was drawn to rat insulin cDNA, yet the claims were drawn to human insulin cDNA. 119 F.3d 1567-1568. However, the specification did not provide adequate written description of human insulin cDNA, as only a prophetic example was provided in which human insulin cDNA was described without any "distinguishing information concerning its identity." *Id.* at 1567. Hence, the written description requirement was not satisfied for the claims drawn to human genes. *Id.*

In *Rochester*, claims were drawn to a method of enzyme inhibition by administration of a non-steroidal compound, but no such compounds were described *at all* in the specification. 358 F.3d 920-921. Hence, the written description requirement for these claims was not satisfied. *Id.*

The claims at issue are unlike those of *Lilly* and *Rochester*, and therefore these cases cannot be used to support a written description rejection of the present claims. Regarding *Lilly*, the present claims regard the same species as described in the specification—specifically, PPT1 modulators that competitively inhibit PPT1. This is unlike *Lilly*, wherein the claimed subject matter differed from that described in the specification. Further, the specification describes numerous examples (and enabling descriptions as well) of subject matter of the rejected claims, as described below. The examples in the specification also set apart the present case from *Rochester*. Whereas the specification in that case provided *no* examples of compounds of the claimed invention, the present specification provides numerous examples of PPT1 modulators of the claimed invention, as described below. Because the claims and the written description described in the present specification do not correlate with the claims and written descriptions as set forth in *Lilly* and *Rochester*, these cases cannot support a written description rejection.

Further, the *Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, Paragraph 1* ("The Guidelines") state that the "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (emphasis added).

The specification recites a sufficient number of species by identifying characteristics, such as physical properties, and sufficient functional features to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Addressing the functional aspect first, Applicants note that claim 1, as discussed herein, has been amended to recite the following: "A method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1." All of the rejected claims depend from claim 1. The functional aspect of these claims is set forth in this claim, as the PPT1 modulators of claim 1 are competitive inhibitors of PPT1. This description is supported by the specification. *See, e.g.*, page 21, lines 3-6 and page 23, lines 5 through 24. Thus, the specification provides a sufficient physical description of the functional aspects of PPT1 modulators as set forth in claim 1, in that they must be competitive inhibitors of PPT1.

The specification also sets forth a sufficient number of species that, when coupled with the identifying characteristics as described above, satisfy the written description requirement. Contrary to the Action's assertion that the specification does not provide a written description of any other specific peptide mimetic that modulates PPT1 other than a peptide mimetic of VKIKK (SEQ ID NO: 12), the specification recites numerous species that may be considered PPT1 modulators. *See, e.g.*, page 6, lines 14-30 (nucleic acid molecules, polypeptides, proteins, peptides, small molecules, antibodies, peptide mimetics); page 7, lines 1-7 (nucleic acid molecules); page 7, lines 9-27 (PPT1 modulators attached to lipid components; chemically modified PPT1 modulators); page 23, line 26 through page 27, line 14 (amino acid variants); page 28, lines 18-20 (peptides corresponding to one or more antigenic determinants of the PPT1 polypeptide).

Further, for each of these species, the specification provides examples of how one of ordinary skill in the art may make and use them. *See, e.g.*, page 6, lines 14-30 (exemplary peptide sequences); page 7, lines 1-7 (variations of nucleic acid molecules); page 21, lines 10-27 (descriptions of proteinaceous molecules as PPT1 modulators); page 23, line 26 through page 27, line 14 (amino acid variants and how to select their design); page 28, line 22 through page 30, line 2 (how to prepare PPT1 modulators that induce an immungenic response); page 30, line 4 through page 40, line 41 (descriptions of lipid modifications of PPT1 modulators).

As mentioned, The Guidelines state: "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by ... disclosure of relevant, identifying characteristics, *i.e.*, ... physical... properties...." The present specification satisfies these requirements with respect to written description support for the rejected claims. In view of the above, Applicants respectfully request reconsideration of these claims and request that the written description rejection be withdrawn.

2. The Enablement Rejection Is Overcome

Claims 1-6, 8-12, 15-25, 27, 32-39 and 42-46 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In particular, it is asserted that undue experimentation would be required to practice the claimed invention, and that the claims are overly broad. Further, it is asserted that one cannot use *in vitro* data to predict *in vivo* results. Applicants traverse.

The *MPEP* states that "the test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *MPEP* §2164.01 (*quoting United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)).

The specification is enabling for methods of inhibiting a cancer cell, such as altering proliferation, metastasis, contact inhibition, soft agar growth, cell cycle regulation, tumor formation, tumor progression, differentiation, programmed cell death, or tumor invasion, using a modulator of PPT1, wherein that modulator is a competitive inhibitor of PPT1. The Action asserts that the specification provides no working examples that demonstrate inhibitory activity of modulators other than cell survival and cell proliferation, and that the specification provides no indication that any PPT1 modulator other than those specifically disclosed (*e.g.*, DAP1) would predictably inhibit an activity of a cancer call grown *in vitro* or found in an animal. However, Applicants note that the provision of working examples is not a requirement. Compliance with the requirements for enablement under 35 U.S.C. § 112 does not require that an example is disclosed, or that the invention be reduced to practice prior to filing. *Gould* v. *Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987) and MPEP §2164.02.

Furthermore, it is well settled that in examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of 35 U.S.C. § 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA 1971). The Examiner has the initial burden of producing reasons that substantiate a rejection based on lack of enablement. *Id.* at 224, 370 (CCPA 1971). *See also* MPEP § 2164.04. The Examiner's burden requires that the Examiner supply a factual basis or scientific principle to reasonably doubt the accuracy of a clear disclosure. *In re Marzocchi*, 439 F.2d at 224. The Examiner, however, failed to provide a factual basis or scientific principle to reasonably doubt the accuracy of the present disclosure. In other words, the Examiner has offered no evidence that the PPT1 modulators of the present

invention would *not* inhibit a cancer cell as claimed. On this basis alone, the rejection should be withdrawn.

The Action also asserts that the *in vitro* data supplied in the specification does not provide enablement for claims drawn to *in vivo* environments. Applicants have supplied, as Exhibit 1, a copy of a Rapid Access to NCI Discovery Resources (R*A*N*D) report dated January 23, 2006. This report relates to the synthesis and *in vivo* testing of DAP derivatives at the National Cancer Institute (NCI). As discussed in the report, doses of 25 mg/kg of the PPT1 modulator DAP1-amide were tolerated when administered to ncr nu/nu (nude) mice via i.v. injection. Further, this dosage gave a serum drug concentration of 70 μM after 2 hours. This level was effective in killing the tumor cells in an *in vitro* assay. Human glioblastoma cells were then grown both subcutaneously and intracranially in mice, wherein intraperitoneal administration at 100 mg/kg/day resulted in no observed toxicity and plasma levels of 100-200 μM were shown at four hours post-dosing. As previous *in vitro* time-course studies indicated that continuous drug levels of 50-100 μM were necessary to inhibit cell growth, these toxicity studies support the use of these compounds *in vivo*.

In view of the above, Applicants respectfully request reconsideration of these claims and request that the enablement rejection be withdrawn.

E. *The Rejection Under 35 U.S.C. § 102(b) Is Overcome*

The Action rejects claims 1-3, 5, 8 and 9 under 35 U.S.C. § 102(b) as being anticipated by Rinehart *et al.* as evidenced by Meng *et al.* Specifically, it is asserted that Rinehart *et al.* teaches a method of inhibiting leukemia cell proliferation comprising administering Didemnin B and that Didemnin B is a proteinaceous compound. It is further asserted, as evidenced by Meng *et al.*, that Didemnin B functions as an agonist that selectively interacts with and inhibits PPT1

activity. In light of the assertion that the present claims are drawn to a method of inhibiting the proliferation of a cancer cell comprising administering to said cell a composition comprising a proteinaceous PPT1 modulator that selectively interacts with and inhibits the activity of PPT1, it is asserted that Rinehart *et al.* as evidenced by Meng *et al.* anticipates the cited claims. Applicants traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants first note that the claims recite the following: "A method of inhibiting a cancer cell comprising administering to the cancer cell a composition comprising a PPT1 modulator in an amount effective to reduce PPT1 activity level, wherein the modulator competitively binds to PPT1." Support for this amendment can be found in the specification and the originally-filed claims. *See, e.g.*, originally-filed claim 4. By making this amendment, Applicants in no way concede that the claim, in its previous form, was anticipated. Applicants reserve the right to prosecute subject matter relating to the amended claim in the same or broader scope in any future application that claims priority to this application.

Meng *et al.* teaches that Didemnin B inhibits PPT1. Meng *et al.*, abstract. However, Meng *et al.* also teaches that Didemnin B noncompetitively inhibits PPT1. The present invention, as evidenced by claim 1, is drawn to modulators of PPT1 that are competitive inhibitors of PPT1. As a result, Meng *et al.* does not teach each and every element of the claimed invention, and thus this reference cannot be anticipatory.

In view of the foregoing, Applicants respectfully request reconsideration of these claims and request that the anticipation rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

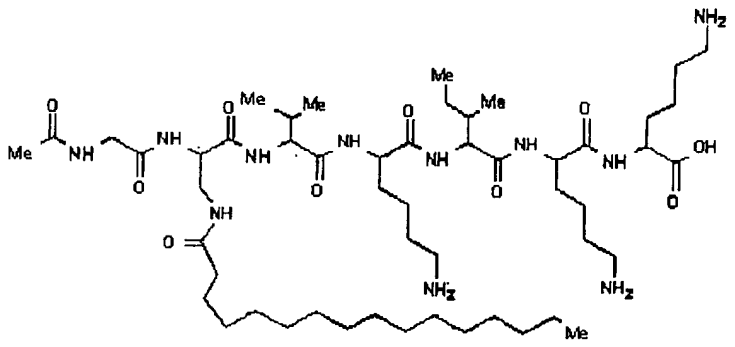
Compound Summary

January 23, 2006

R*A*N*D Initiative

NSC D716553 Discreet (PPT1 Inhibitors - DAP1)

D716553



Molecular Weight: 1038 **Msds:**

Common Name: Discreet (PPT1 Inhibitors - DAP1) **Chemical Name:**

CAMT: 5.6mg

Related NSCs

D725284

Molecular Weight:1394

Common Name: Discreet (PPT1 Inhibitors - DAPKA) **Chemical Name:**

CAMT: 376mg

D726020

Molecular Weight:1380

Common Name: Discreet (PPT1 Inhibitors - DAP1-Amide) **Chemical Name:**

CAMT: 345mg

Summary

Agent Category: **Description:**

Abstract:

Year entering Clinic: **Current Branch Involved:** DSCB

Comments: Projected Dates for Investigator's Seminars/Meetings:

Cycle: 3

Principal Investigator: Glyn Dawson **Affiliation:** University of Chicago

Compound Summary

January 23, 2006

R*A*N*D Initiative

NSC D716553 Discreet (PPT1 Inhibitors - DAP1)

Application Receipt Date: 01-OCT-2001 **BRB Oversight Date:** **Review Date:** 30-NOV-2001

Project Name: Palmitoyl:Protein Thioesterase (PPT1) Inhibitors as Antitumor Drugs

Project Summary: In a test of the hypothesis that overexpression of palmitoyl:protein thioesterase 1 (PPT1) protects cells against apoptosis, the applicant proposes that existing inhibitors of PPT1 be evaluated in vitro and in vivo for antitumor activity. In addition, the applicant proposes that resources be utilized to design and synthesize more potent inhibitors based on suggested molecular characteristics.

Approved Support: Small-scale synthesis of PPT1 inhibitors, DAP1 and DAP1-KA, evaluation of DAP1 and DAP1-KA in in vitro and in vivo tumor model systems, and pharmacokinetic analysis of DAP-1 and DAP1-KA.

New Action Items

Ongoing Action Items

- Dr. Stinson will develop assay and do PK studies, quantities of DAPKA permitting (09/03).
- Based on quantity and cost of synthesis of DAP1-KA required for hollow-fiber testing, determine if a review of the status of the project is mandated (09/03).

Small-Scale Synthesis (DSCB)

DAP1-KA has a ketoamide unit incorporated in the structure, instead of the unsubstituted side-chain. The synthesis of the two compounds has been assigned to two different contractors. These contractors are Stanford Research Institute and Research Triangle Institute. They are currently obtaining the starting materials. The synthesis of the compounds is estimated to take 3 months (05/02).

Approximately 500 mg of DAP1-KA have been synthesized by the contractor and are in the process of being purified (09/02).

The procedures for the multi-step synthesis of both DAP1 and DAP1-KA have been worked out. There are 600 mg of DAP-1 and 110 mg of DAP1-KA available for the 60-cell line screen testing. The synthesis of larger quantities (2 g) of the compounds for in vivo testing is underway (01/03).

A total of about 550 mg of the DAP1-KA has been synthesized and is i the repository (09/04).
No additional synthesis is planned at this time (09/04).

In Vivo Activity (BTB)

Maximum Tolerated Dose: 400 mg/kg. NSC 726020 was administered as an IP bolus in a vehicle of 10% DMSO/90%Saline+Tween 80. The compound was listed as a homogeneous smooth suspension.

725284 (DAPKA)

NSC 725284 was given to ncr nu/nu (nude) mice by i.v. injection at doses of 100 or 50 mg/kg, and by i.p. injection at a dose of 100 mg/kg. The vehicle for the i.v. study was DMSO (dose volume 1 ml/kg), and for the i.p. study was sterile water (dose volume 4 ml/kg). Heparinized plasma was collected from mice at selected intervals from 5 through 120 minutes after i.v. injection, and 5 minutes through 24 hours after i.p. injection, and plasma concentrations of NSC 725284 were determined by HPLC-MS.

Plasma concentrations of NSC 725784 declined in a mono-exponential manner following i.v. injection. Levels were 200 µM 5 minutes after injection of 200 mg/kg, decreasing with a half-life of 4 hours to 140 µM by 120 minutes. This i.v. dose was

toxic to the mice. I.v. injection of 50 mg/kg produced concentrations of 100 µM after 5 minutes, decreasing with a half-life of 2 hours to 50 µM by 120 minutes. Following i.p. injection of 100 mg/kg, peak plasma concentrations slightly over 100 µM NSC 725284 were attained after 2 to 4 hours. Levels then decreased with a half life of 115 hours to 45 µM by 24 hours.

NSC 726020 (DAP1-amide)

NSC 726020 was given to ncr nu/nu (nude) mice by i.v. injection at doses of 50 or 25 mg/kg, and by i.p. injection at a dose of 50 mg/kg. The vehicle for the i.v. study was DMSO (dose volume 1 ml/kg), and for the i.p. study was sterile water (dose volume 4 ml/kg). Heparinized plasma was collected from mice at selected intervals from 5 through 120 minutes after i.v. or i.p. injection, and plasma concentrations of NSC 726020 were determined by HPLC-MS.

I.v. injection of NSC 726020 at a dose of 50 mg/kg was lethal to the mice. A dose of 25 mg/kg was tolerated, and produced plasma concentrations of approximately 70 µM throughout the 2-hour period of study. Following i.p. injection of 50 mg/kg plasma levels increased from 6 µM after 5 minutes, to 74 µM by 120 minutes.

Seminars and Meetings

Meeting Date: 02-NOV-2004 PI Tele/Video Conference

Presenter: **Organization:**

Meeting Date: 29-SEP-2003 PI Tele/Video Conference

Presenter: **Organization:**

Synthesis of sufficient quantities of the desired compound for in vivo studies may not be feasible with the current budget and timetable.

Other Notes

DAP1-KA was tested in the 60-cell line screen and at 100 µM, its activity was superior to that of NSC 716553D, the compound sent by the PI (04/03).

PI made 5 mg of compound - most efficient synthesis procedure unknown. NCI has 500 mg of impure compound which can be purified by chromatography. Pharmacology and MTD will be conducted to determine whether 500 mg will provide enough purified material to conduct hollow-fiber testing. If studies show that material is suitable, additional monies will be committed to purify the 500 mg (12/03).

NCI will support spending additional money to purify DAP1-KA (process will take a few months). Compound 726020 showed no activity in the time course assay. Compound 725284 tested in serum - highly soluble in ethanol (needs to use DMSO as initial solvent, 100 FCS helpful in solubilizing). Good activity in time-course assay (needs to have long exposure). Leukemias, Jurkat lines are most sensitive (01/04).

Purification of DAP1-KA is underway. Formulation is an issue, as any addition of aqueous solvent to a DMSO solution causes precipitation of the compound. An expert in liposomal preparations will be at EPN on March 24, and may be interested in taking on a molecule such as DAP1-KA as a project (03/04).

The synthesis and purification of DAP1-KA should be completed by June of this year. Once the sample is in hand, the best use of the sample will be determined (04/04).

Synthesis and purification of DAP1-KA have resulted in the delivery of sufficient amounts of material for performing the PK

studies. Once the data become available, appropriate in vivo studies will be designed (06/04).

Dr. Stinson presented the PK values obtained from his experiments with DAPKA (NSC 725284) and DAP1-amide (NSC 726020). For DAPKA, a dose of 100 mg/kg, administered i.v., peaked at 4 hours reaching a 100 µM concentration. This concentration is very close to the levels that are toxic to the animals. At 24 hours, the concentration was approximately 40 µM. DAP1-amide administered i.v. was toxic at 50 mg/kg, but was tolerated at 25 mg/kg–a dose which achieved a peak concentration of 70 µM at 2 hours post injection. Previous in vitro time-course studies indicated that continuous drug levels of 50-100 µM were necessary to inhibit cell growth. A conference call with Dr. Dawson will be scheduled in order to discuss the planning of additional studies (08/04).

A teleconference is planned for November 2, 2004, where additional studies, such as the hollow-fiber assay, will be suggested (10/04).

During the teleconference on November 2, DTP agreed to test the compound in an orthotopic neuroblastoma tumor model using either U373 or U87-MG tumor cell lines. The PI has provided the tumor cell lines to Dr. Hollingshead. To test the doses indicated as necessary in the preliminary studies performed by the PI, Dr. Stinson has been asked to conduct a dosing study using repeated dosing at 24-hr intervals to determine whether the mice can tolerate such a schedule. Tolerance of the higher dose will be a prerequisite for carrying out the tumor model study (11/04).

Dr. Stinson is conducting repeat-dosing studies, and Dr. Hollingshead is MAP testing the U373 cells received from Dr. Dawson's group (12/04).

The U373 MAP test is complete. BTB initiated the growth assays with both s.c. and intracranial tumor implantation. Currently, the s.c. tumor is growing and is at day 12. Tumor growth cannot be assessed for the i.c. implant at this point, because the endpoint is morbidity. However, the mice look fine and are gaining weight. Data should be available within this month and potential in vivo efficacy studies can be discussed (02/05).

Dr. Hollingshead reported that the U373 cells are growing intracranially. She should soon be able to begin the xenograft study (03/05).

Dr. Stinson is beginning his studies and should have data available at the May R*A*N*D meeting (04/05).

Dr. Stinson has completed multi-dose testing in mice with NSCs 725284 and 726020. Animals were treated i.p. at a dose of 100 mg/kg/day for three days. No evidence of toxicity was observed. Plasma levels, 4 hours post dosing, were in the 100-200 µM range. Dr. Hollingshead reported that the growth curves for s.c. implants of the U373 cells were acceptable, but the i.c. implants did not perform as well. A study using the s.c. implants is advisable (08/05).

A subcutaneous xenograft experiment with U373 cells has been devised and is in the queue (01/06).